Retinopathy of Prematurity: Risk Factors and Role of Antenatal Betamethasone in Indian Preterm Newborn Babies

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──────── **ABSTRACT** ────────

Background: Increase in the survival of preterm neonates has led to increased incidence of retinopathy of prematurity (ROP). Among various risk factors, only prematurity is well-established and role of others is still not clear. Effect of antenatal betamethasone on ROP severity is also controversial. Available literature from India has a paucity of information. **Objectives:** (a) The primary aim of the following study is to find the incidence and risk factors of ROP and (b) secondary aim is to assess the effect of antenatal betamethasone on ROP. **Design:** prospective, observational cohort study. **Setting:** Tertiary level neonatal care unit. **Materials and Methods:** A total of 148 infants ≤34 weeks gestation at birth, completed the study protocol. Severe ROP was defined as stage II and higher (including plus disease) of ROP. Various perinatal factors including antenatal betamethasone were analyzed by univariate followed by multivariate analysis. **Results:** overall incidence of ROP (any stage) was 44.6%. Severe ROP was mainly detected in <1200 g birth weight and/or <30 weeks gestational age. Antenatal betamethasone was associated with non-severe form of ROP ($P < 0.05$) on univariate analysis, but could not pass multivariate logistic regression analysis. Among other perinatal factors studied, low birth weight (<1200 g) (odds ratio [OR]: 19.699, 95% confidence interval [CI]: 2.42-160.17, $P = 0.005$), low gestational age (<30 weeks) (OR: 36.52, 95% CI: 3.76-354.3, $P = 0.002$), acidosis (OR: 6.932, 95% CI: 1.16-41.33, $P = 0.034$) and blood transfusion (OR: 14.11, 95% CI: 1.494-133.5, $P = 0.021$) were associated with babies in severe ROP in an independent manner. **Conclusions:** Low birth weight and low gestational age emerged as independent significant risk factors along with blood transfusion and acidosis. Antenatal betamethasone may be preventive for severe ROP. More studies are however recommended.

Key words:
Antenatal betamethasone, retinopathy of prematurity, risk factors, severity

INTRODUCTION

The magnitude of retinopathy of prematurity (ROP), a potentially blinding disorder, has been observed to be rising primarily due to improved survival of preterm babies and increasing expertise in its early recognition.[1,2] Very low birth weight and low gestational ages have consistently been associated with severe ROP.[3-5] The association of ROP with various risk factors has been analyzed in different studies yet firm conclusions have not been made.[4-6] Antenatal steroids have found definite place in prevention of various morbidities associated with prematurity like respiratory distress syndrome (RDS), intraventricular hemorrhage (IVH),[7] but their effect on ROP is still not clear. Few western studies have found antenatal steroids to be protective for severe ROP forms,[8-10] while others have failed to find any effect on ROP severity.[11,12] However, its impact (positive or negative) on ROP is still unclear.

Hence, the study was planned out to find the incidence, perinatal factors (including antenatal betamethasone) associated with ROP, in a prospective manner in Indian babies (<34 weeks gestation), to add to the existing literature and knowledge.

MATERIALS AND METHODS

This prospective, observational cohort study was carried out for 12 months duration. Ophthalmologist, who performed ROP examination, was unaware of the perinatal course of babies. For this study, perinatal data of all surviving infants ≤34 weeks gestation at birth were collected. Babies

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were examined after a prior informed and written consent from attending parents. Ethical clearance was obtained from institute ethics committee prior to start of the study.

Data collection and recording

Data regarding maternal factors including steroid administration were collected from maternal records. All the post-natal events were carefully recorded from the infants' admission records. During an ophthalmic examination, the staging of eyes was done using international classification of ROP.[13] All perinatal data (including the ROP status) collected from each infant and maternal medical records were fed into a standardized data collection sheet for the purpose of this study. Antenatal betamethasone was used at the full discretion and judgment of attending obstetrical staff in an internationally standardized manner. Effective antenatal steroid exposure was defined as 12 mg of betamethasone given intramuscular for two doses, 24 h apart with the last dose given at least 12 h prior to delivery.

Screening and follow-up

In our unit, initial screening is performed as per screening criteria for ROP published in India, which recommends screening of all babies <32 weeks gestation.[14] These criteria recommend examination of babies >32 weeks also, though in selected cases. As antenatal betamethasone is given up to 34 weeks gestation cases, we included data of babies 32-34 weeks gestation as well, for this study. For the purpose of examination, the pupils of eyes were dilated using a mixture of phenylephrine (2.5%) and tropicamide (0.5%) instilled 3 times at 15 minutes interval, 1 hour prior to the examination. Indirect ophthalmoscopy of whole retina was performed with +20 diopter lens. Scleral indenter was used to help in looking at retinal periphery. The infants were called for further follow-up depending on the stage of ROP detected at first and each further examination. Duration of screening follow-up in the initial phase progressed till ROP reached treatable stage or regressed completely. In severe forms of ROP, surgical intervention was employed in the form of laser photo-coagulation.

Statistical analysis

Various perinatal factors including antenatal betamethasone exposure were studied. ROP not only can progress to severe acute events like retinal detachment, but is also known to produce long-term complications such as myopia and strabismus.[15] As published literature suggests that stage I ROP resolves without any significant long term sequelae[15] and hence main outcome measure "severe ROP" was defined as any ROP stage II and higher, including severe forms like plus disease (which are associated with significant acute and long-term sequelae. Cases with no ROP or non-progressive stage I were categorized as "non-severe ROP". Continuous

data were analyzed employing Student's *t*-test. Qualitative data were analyzed employing Pearson's Chi-square test with/without Yate's correction. All data were entered into a spreadsheet and analyzed using statistical software (IBM, SPSS 20, Chicago, IL, USA). Univariate and multivariate logistic regression was done for various risk factors and antenatal betamethasone for development of severe ROP. *P* < 0.05 was considered to be statistically significant. Odds ratio and 95% confidence intervals were calculated for independent factors.

OBSERVATIONS AND RESULTS

In the study period, 182 eligible neonates got registered in the study and 148 completed the study protocol duration. The mean birth weight was 1494.0 ± 0248 g (800-1900 g), mean gestation age was 31.682 ± 1.5468 weeks (27-34 weeks) [Table 1] and the overall male: female ratio was 1.3125:1 (84:64). Figure 1 shows the overall ROP case distribution. Out of 86 neonates <1500 g birth weight, 57 (66.2%) developed ROP. Severe ROP cases (stage II and higher) were present mainly in the babies with <30 weeks gestational age and 1200 g birth weight.

Univariate analysis for various risk factors and antenatal betamethasone, by Student's *t*-test (for continuous data) and Pearson's Chi-square analysis (for discrete data) revealed results as given in Table 1. Oxygen fluctuation, acidosis, low birth weight, low gestation, RDS, IVH, blood transfusion, prolonged oxygen were found significant (*P* < 0.05).

Table 1: Baseline variables and univariate analysis for antenatal betamethasone and risk factors for severe ROP

Variable	Non-severe ROP (*N*=117)	Severe ROP (*N*=31)	*P* value
Oxygen fluctuation[#]	12	9	0.0004
Acidosis (pH<7.2)	39	25	0.0001
Sepsis	33	14	0.1127
Blood transfusion*	2	19	0.0001
Exchange transfusion	10	10	0.0006
Anemia	11	8	0.0512
Intra-uterine growth retardation	49	12	0.9095
Intraventricular hemorrhage	9	15	0.0001
Mechanical ventilation	10	10	0.006
Birth asphyxia[$]	23	11	0.1047
RDS	52	26	0.0001
Prolonged oxygen (>28 days)	59	29	0.0001
Antenatal betamethasone	48	6	0.0435
Birth weight (grams mean±SD)	1590.7±177.5	1098.7±184	0.0001
Gestation (weeks mean±SD)	32.3±1.27	29.3±1.05	0.0001

*Transfusion of packed RBC (10 cc/kg body weight or more) at any time in first 4 weeks of life, [$]Apgar score<3 at 5 min of life, [#]More than three episodes of oxygen saturation falling below 87% by transcutaneous oxygen saturation (SpO$_2$) requiring assistive oxygen support OR more than three episodes of SpO$_2$ fluctuation >10% on any assistive oxygen support, in any continuous 24 h time period. ROP – Retinopathy of prematurity; RDS – Respiratory distress syndrome; SD – Standard deviation; RBC – Red blood cell; SpO2 – Oxygen saturation

In univariate analysis (on Pearson's Chi-square test), the *P* value of 0.0435 implied possible protective role of antenatal betamethasone in preterm deliveries for severe ROP. Figure 2 gives stage wise profile of ROP incidence in steroid exposed and non-exposed babies. Babies with stage II and higher ROP, but exposed to antenatal steroids, however, did not develop threshold ROP or ROP requiring surgery. Multiple-variate logistic regression analysis [Table 2] was performed for antenatal betamethasone and the risk factors found significantly associated with severe ROP (stage II and

higher) in univariate analysis. Low gestation (<30 weeks), low birth weight (<1200 g), blood transfusion and acidosis emerged as independent significant risk factors. Antenatal betamethasone was not found as an independent factor affecting ROP, in multivariate regression analysis.

A total of eight cases underwent surgical treatment. None of the babies, who were exposed to antenatal steroids, reached the operable stage. There were three cases of stage III ROP with threshold disease and two cases of stage IV ROP.

DISCUSSION

ROP has shown a rise in incidence in developed nations as well as developing countries like India.[1-5] The overall incidence in the present study on 148 preterm neonates with <34 weeks gestational age was 44.6% and 66.2% babies <1500 g birth weight developed ROP. In a recent study from Kuwait, authors found a similar incidence of ROP.[6] Our hospital being a referral center catering to a large area, receives cases referred in a very sick condition. Pregnant female patients come mostly in a very sick profile of conditions. High incidence of ROP in our study can be attributed to overall very sick profile of our study cases. Furthermore, newborn care system in western countries is highly advanced as compared to a developing country like India, which undoubtedly creates a difference between the outcomes of neonates.

Significant ROP cases in gestation >32 weeks have also been reported.[2,16] Hence, for these two reasons, we took the cutoff of ≤34 weeks gestational age as a criterion of ROP screening. The incidence of ROP in our babies in 32-34 weeks gestational age babies was negligible (only five babies with stage I ROP with regression) while it was 59% (any stage) in 30-32 weeks group. Incidence in our study was thus more with decreasing gestational age, in agreement with other studies.[1-6]

Various risk factors were analyzed for their correlation with severe ROP (stage II or higher) category. Thus, our analysis is relatively specific for the severe forms of ROP. On univariate analysis, many risk factors were found to be significantly linked to severe ROP [Table 1]. Out of all these, on subsequent multiple variate logistic regression analysis, blood transfusions and acidosis were found to be an independent risk factors for ROP besides low gestational age and birth weight [Table 2].

Present study found low birth weight and gestational age, as independent significant risk factors in agreement with the previous few studies of similar selection criteria.[4-6,14] In our study too, the severe ROP was mainly present in <30 weeks gestation and <1200 g birth weight. All the babies
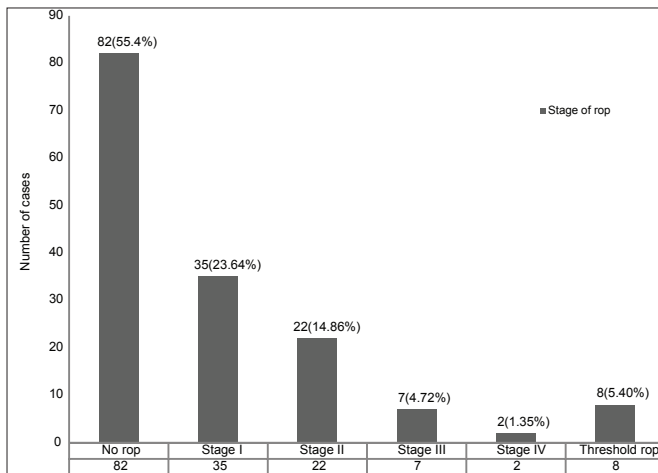

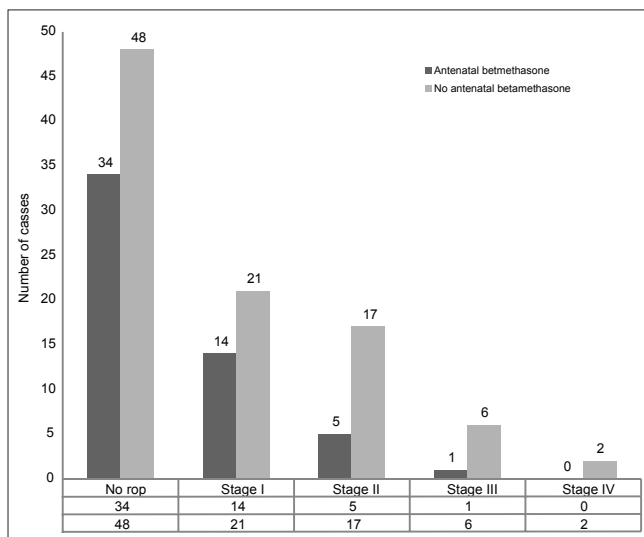**Figure 1:** Overall retinopathy of prematurity distribution (stage wise)

Figure 2: Retinopathy of prematurity distribution according to antenatal betamethasone exposure

Table 2: Multivariate logistic regression analysis

Variable	*P* value	Odds ratio (adjusted)	95% confidence interval
Birth weight (<1200 g)	0.005	19.699	2.423-160.172
Blood transfusion	0.021	14.11	1.494-133.33
Acidosis	0.034	6.925	1.160-41.33
Low gestation (<30 weeks)	0.002	36.52	3.761-354.653

with <1000 g birth were affected (ROP any stage), in our study. Thus, our study is in agreement with available western and Indian literature.

In our study, blood transfusion emerged as an independent risk factor for severe ROP. Three other Indian studies by Chaudhary *et al*., Dutta *et al*., and Maheshwari *et al*., also found blood transfusions as an independent risk factors.[2,16,17] In a western study, Hessel *et al*., showed that blood transfusion volume and iron load by transfusions are associated with the risk of occurrence of ROP in infants with a birth weight of <1250 g.[18] Although, the exact role of blood transfusion in ROP is thus not clear in Indian and western literature, with an apparent trend of more ROP with the association of blood transfusion, the nurseries all over the world are now using blood in a restricted manner. Brooks *et al*., however, did not find any difference in ROP status on liberal (maintaining >40% hematocrit) versus restricted (need based) transfusion protocol.[19] Thus, exposure to blood of adult type, in preterm babies, itself may be causative of ROP in a dose independent manner. It would need further studies to establish the role of blood transfusion in relation to ROP.

Acidosis appeared to be an independent risk factor for severe ROP in the present study. It has been proven in an animal study that metabolic acidosis, in pure fashion causes severe ROP.[20] Our results are in agreement with western study by Prendville and Schullenberg, having a comparable sample size.[21] In an Indian study, Maheshwari *et al*., however, did not find acidosis to be a significant risk factor.[17] It was a study of smaller size and bigger infants up to 35 weeks were included whereas acidosis is more common in very preterm neonates. The difference in the study group possibly explains the difference in results. Furthermore, acidosis as a criterion has not been studied primarily in many Indian studies. Whether acidosis affects ROP needs further scientific exploration.

There is a paucity of literature on the effect of antenatal steroids on ROP. Effect of antenatal betamethasone on ROP is still not clear. Previous few western studies have given conflicting reports.[8-12] Lee *et al*., in their study have reported a favorable (although statistically non-significant) trend of ROP in babies exposed to antenatal betamethasone as compared to dexamethasone.[10] In the present study, on univariate analysis, antenatal betamethasone administration was found to have a protective effect for ROP. None of the babies even falling in severe ROP category (i.e., stage II and higher ROP), who were exposed to antenatal betamethasone, developed ROP requiring surgery [Figure 2]. However, on multivariate logistic regression analysis, antenatal betamethasone was not found significant. As the risk factors,

prematurity and antenatal steroids are highly inter-twined variables, whether antenatal betamethasone protects from severe ROP is subject to further scientific exploration.

Strengths of the study

(a) To best of our knowledge, our study is first of its kind from India, which assesses the role of antenatal steroids in relation to ROP. Moreover, (b) our study is specific for association of risk factors and antenatal betamethasone with severe ROP forms (stage II and higher).

Limitations of our study

Our study has some limitations. In our study, extremely low birth weight neonates formed only a small fraction of participating babies. Thereby, exact incidence can be affected in our analysis in comparison to other centers. Also, long-term follow-up of the neonates has not been included in the present study analysis.

CONCLUSIONS

Government hospitals like ours, catering to poor economic strata may have a high incidence of ROP. Low birth weight and gestation age are again proved to be significant factors for stage II and higher ROP. A statistically non-significant trend suggests possible protective role of antenatal betamethasone. Though antenatal steroids will continue to be used for prevention of RDS and other morbidities, its effect on ROP is subject of further scientific exploration. We conclude to recommend more studies, to evaluate the various risk factors and role of antenatal betamethasone in preterm neonates of India.

ACKNOWLEDGMENT

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